Remarks

Claim status. Claims 1, 28-33, 36, 37 and 39 to 41 are now in the case. All pending claims are amended hereby. Claims 27, 34, 35, and 38 have been canceled due to the withdrawal from consideration as unelected subject matter.

The amendment to the first paragraph presents within the specification the priority already claimed. The amendment to Claim 1 incorporates subject matter from canceled Claim 27. The remaining claim amendments merely correct the dependency due to cancellation of Claim 27. Accordingly, no new matter is added by any of the amendments.

Rejection under Section 102(e). The rejection under Section 102(e) was based on U.S. Pat. No. 5,605,690 to Jacobs *et al.* The Examiner alleged that this patent taught combination therapy with a TNF antagonist and IL-1R and/or IL-2R. As amended, the present application does not claim combination therapy with IL-1R or IL-2R. Thus, the Jacobs patent does not anticipate the present claims.

Rejection under Section 103. The Examiner based the rejection under Section 103 on Jacobs *et al.* further in view of U.S. Pat. No. 5,633,145 (Feldmann *et al.*); Anderson *et al.* (1996), J. Clin. Invest. 97(11): 2672-9; and Hubbard *et al.* (1996), Arth. & Rheum. 39(9): S226.

The Applicants note that the Examiner mischaracterized Jacobs *et al.* in the statement, "Jacobs *et al.* do *not* teach that the TNF binding protein may be the sTNF-RII...." (Office Action at page 4, emphasis added). The Jacobs *et al.* patent does teach sTNF-RII --see, for example, col. 4, lines 24-26. Jacobs *et al.* do not, however, teach combination with a COX2 inhibitor.

The Examiner misstated the content of Feldmann *et al.* with the statement, "Feldmann *et al.* disclose the TNF binding protein sTNF-RII (SEQ ID NO: 25), that is 100% identical to SEQ ID NO: 4 of the instant application...." (Office Action at page 4). According to the Feldmann patent itself, its SEQ ID NO: 25 provides the sequence of "TNFα" (col. 2, line 10-11). SEQ ID NO: 25 of the Feldmann *et al.* patent appears, however, to be an sTNF-RI sequence (*cf.* SEQ ID NO: 25 of Feldmann *et al.* and SEQ ID NO: 2 of the present application). Feldmann *et al.* also do not teach combination with a COX2 inhibitor.

The Examiner noted that Anderson *et al.* teaches that COX2 plays a prominent role in the inflammation associated with adjuvant arthritis and that COX2-derived prostaglandins upregulate COX2 and IL-6 expression at inflammatory sites. (Office Action at page 4). The Examiner summarized Hubbard *et al.* as teaching that a COX2-selective inhibitor is effective as a treatment for

osteoarthritis. Anderson *et al.* and Hubbard *et al.* both fail, however, to suggest combination with a TNF inhibitor.

The Examiner reads the aforementioned prior art as teaching two different pathways involved in inflammation, leaving the skilled artisan motivated to combine agents because "inhibiting two pathways involved in inflammation would be more effective than inhibiting just one pathway with a single drug, and such a combination therapy could also have synergistic effects." (Office Action at page 5).

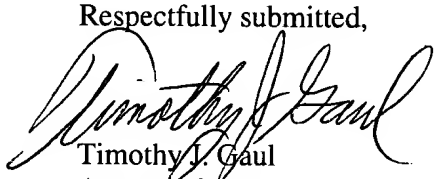
Contrary to the examiner's interpretation, one could read the cited references as somewhat opposing. The Anderson paper notes that, although TNF-α is upregulated in arthritic synovial tissue, the only drug tested in the reference had no effect on TNF-α levels. Based on the Anderson paper, one could suspect that upregulation of TNF-α is not a major factor in the arthritis model tested, or that TNF-α might not be a good drug target because it did not have any role in prostaglandin production.

One could also read the cited references as directed toward alternative conditions. The references employ different models (*Cf.* Anderson *et al.* at page 2573 and Examples 4 to 6, cols. 17 to 20, of Jacobs *et al.*). One could speculate from these references that TNF binding proteins and COX2 inhibitors are active against different models and perhaps ultimately different forms of arthritis.

In summary, none of the references cited suggests combining a TNF binding protein and a COX2 inhibitor. Feldmann *et al.* and Jacobs *et al.* describe effects of TNF binding proteins, while Anderson *et al.* and Hubbard *et al.* describe effects of COX2 inhibitors. With no suggestion for combination among them, one could read these references as presenting distinct, perhaps opposing, views on how to treat inflammatory diseases. Alternatively, given the different experimental models employed, one could read these references as suggesting different treatments for different models of arthritis and, ultimately, different forms of arthritis.

Conclusion. In light of the foregoing amendments and remarks, the Applicants respectfully request reconsideration of all grounds for objection and rejection, entry of all amendments and allowance of all claims.

Respectfully submitted,



Timothy J. Gaul
Attorney for Applicants
Registration No.: 33,111
Phone: (805) 447-2688
Date: May 7, 2003

Please send all future correspondence to:

US Patent Operations/ [TJG]
Dept. 4300, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

VERSION SHOWING CHANGES

Page 1, line 3:

This application is a divisional of application Serial No. 09/326,394 filed June 4, 1999, now United States Patent No. 6,306,820, which is a continuation of PCT/US97/22733, filed December 8, 1997, which claims benefit to U.S. Provisional Serial No. 60/032,587, filed December 6, 1996, U.S. Provisional Serial No. 60/036,355, filed January 23, 1997, U.S. Provisional Serial No. 60/039,315, filed February 7, 1997 and U.S. Provisional Serial No. 60/052,023, filed July 9, 1997, all of which are hereby incorporated by reference.

Amended Claims:

1. A method for treating an acute or chronic inflammatory disease which comprises administering to a patient in need thereof therapeutically effective amounts of a TNF binding protein and at least one COX2 inhibitor~~additional anti-inflammatory drug~~, wherein said TNF binding protein and COX2 inhibitor~~additional anti-inflammatory drug~~ are administered separately or in combination and wherein the adminstration of the TNF binding protein is prior, concurrent, or post-administration of the COX2 inhibitor.

28. The method of treatment according to claim 1 ~~27~~, wherein the COX2 inhibitor is celecoxib.

29. The method of treatment according to claim 1 ~~27~~, wherein the acute or chronic inflammatory disease is a TNF-mediated disease.

30. The method of treatment according to claim 1 ~~27~~, wherein said TNF binding protein comprises a sequence which is at least about 80% homologous to the amino acid sequence of SEQ ID NO: 2 or to the amino acid sequence of SEQ ID NO: 4.

31. The method of treatment according to claim 1 ~~27~~, wherein said TNF binding protein comprises a sequence which is at least about 90% homologous to the amino acid sequence of SEQ ID NO: 2 or to the amino acid sequence of SEQ ID NO: 4.

32. The method of treatment according to claim 1 ~~27~~, wherein said TNF binding protein comprises a sequence which is at least about 95% homologous to the amino acid sequence of SEQ ID NO: 2 or to the amino acid sequence of SEQ ID NO: 4.

33. The method of treatment according to claim 1 ~~27~~, wherein said TNF binding protein comprises a sequence which is at least about 99% homologous to the amino acid sequence of SEQ ID NO: 2 or to the amino acid sequence of SEQ ID NO: 4.

36. The method of treatment according to claim 1 ~~27~~, wherein said TNF binding protein is non-glycosylated.

37. The method of treatment according to claim 1 ~~27~~, wherein said TNF binding protein is glycosylated.

39. The method of treatment according to claim 1 ~~27~~, wherein said TNF binding protein is produced by recombinant DNA methods.

40. The method of treatment according to claim 1 ~~27~~, wherein said inflammatory disease is an inflammatory disease of a joint.

41. The method of treatment according to claim 1 ~~27~~, wherein said inflammatory disease is rheumatoid arthritis.